REMARKS/ARGUMENTS

1. Status of the Claims

Claims 1-22 are currently pending.

Claims 12 and 15 are currently amended.

Claim 12 has been amended to include the more than 10 language as supported by the specification and claims of record, as well as Examples 12-15.

Claim 15 has been amended to correct the spelling of the word multilamellar.

No new matter has been added.

2. Claim Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 12 is rejected under 35 U.S.C. § 112, second paragraph allegedly as being indefinite because the oligonucleotide length recited in claim 12 allegedly conflicts with the oligonucleotide length recited in claim 1, from which claim 12 depends. It is believed that the present rejection is moot in view of the amendments to claim 12 herein to direct claim 12 to oligonucleotides in the range of more than 10 to about 100 nucleotides in length.

3. Claim Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph allegedly as failing to comply with the written description requirement. Applicants have carefully reviewed the statements of the rejections in the present Office Action mailed June 15, 2007 (hereinafter, the Office Action) and in the Office Action mailed January 4, 2007 and respectfully traverse because no *prima facie* case of an inadequate written description is presented.

The Examiner asserts that allegedly the instant claims embrace an enormous number of oligonucleotide lacking CpG motifs, constituting a genus, and that allegedly the specification fails to disclose a representative number of the numerous ribonucleotides, deoxyribonucleotides or chemically modified oligonucleotides of any size or sequence composition, lacking CpG motifs, that elicit a therapeutic systemic, non-antigen specific immune response (see the Office Action at page 3, lines 16-21). The Examiner further asserts that the

specification allegedly does not describe the structure or functional nature of the numerous oligonucleotides, other than a single distinct sequence of a 25mer, 50mer, 75mer and a 100mer (see, page 3, lines 22-24 of the Office Action (which actually are 4 oligonucleotides, not a single distinct sequence)). The Examiner still further asserts that allegedly the specification is silent on the specific characteristics, or sequence motifs of any non-CpG oligonucleotide that may contribute to a therapeutic response (see, page 3, lines 24-26 of the Office Action).

Applicants respectfully disagree with each of the Examiner's assertions for the reasons on record and for the following reasons.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." See MPEP § 2163.02 and the court decisions cited therein (MPEP 8th Ed., Rev. 6, Sept. 2007).

The claimed invention is directed to compositions, and methods of use thereof, for elicitation of a systemic, non-antigen specific immune response in a mammal comprising: a liposome delivery vehicle; and an oligonucleotide containing no CpG motifs, and from more than 10 to about 500 nucleotides in length; wherein the composition elicits a systemic, non-antigen specific immune response in the mammal.

The size range of the claimed oligonucleotide(s) being greater than 10 to about 500 nucleotides in length is described in numerous places in the specification including, for example, paragraphs [0012] and [0107].

Furthermore, the specification describes the claimed invention in numerous additional places including, for example, in paragraph [0107], by stating, "Immune activation by nucleic acid:lipid complexes of the present invention can be induced by eukaryotic as well as prokaryotic nucleic acids, indicating that there is some property of the nucleic acid:lipid complexes that is inherently immune activating, regardless of the source of the nucleic acids." (Emphasis added.) Thus, persons of ordinary skill in the art would recognize that the Applicants invented what is claimed because the specification clearly describes the claimed invention. It is Applicants assertion that non-CpG nucleic acid:lipid complexes elicit a systemic, non-antigen specific immune response in a mammal as described in the specification and the Examiner

provides no objective evidence to establish that there is a lack of description of the claimed invention in the specification.

The Examiner's assertion that allegedly the specification fails to disclose a representative number of the numerous ribonucleotides, deoxyribonucleotides or chemically modified oligonucleotides of any size or sequence composition, lacking CpG motifs, that elicit a therapeutic systemic, non-antigen specific immune response, is incorrect and misapplied. The present assertion is incorrect because the Examiner has failed to provide objective evidence that the species disclosed in the specification are not representative of the claimed genus. The present assertion is misapplied because Applicants are not required to know the mechanism by which their invention works. For example, the Examiner apparently desires the disclosure of specific base sequences that are immunogenic. However, the Examiner is making an unfounded assumption, lacking objective evidence, that the mechanism by which the claimed composition stimulates the immune response is due to the specific order of the bases in the oligonucleotide. There are many structural features of the claimed oligonucleotide:liposome composition that can account for the elicitation of the claimed immune response. For example, the claimed oligonucleotides have phosphate backbones, sugar moieties, nucleoside residues, and secondary or higher order structure. The higher order structure of the oligonucleotides may be impacted by the presence of the liposome delivery vehicle, for another example. Any of the structures may participate in the elicitation of the claimed immune response. Importantly, Applicants are not required to explain the mechanism of action of their invention to meet the written description requirement. Applicants are only required to clearly describe the claimed invention to allow persons of ordinary skill in the art to recognize that he or she invented what is claimed. The specification provides such written description as discussed on the record and above. Meanwhile, the Examiner has failed to establish a prima facie case of lack of written description as set forth by Applicants arguments on the record and above. Accordingly, the present rejection may properly be withdrawn.

4. Claim Rejections Under 35 U.S.C. § 112, First Paragraph - Lack of Enablement

Claims 1-22 are rejected under 35 U.S.C. § 112, first paragraph allegedly as failing to comply with the enablement requirement. Applicants have carefully reviewed the statements of the rejections in the present Office Action and in the Office Action mailed January 4, 2007 and respectfully traverse because no *prima facie* case of lack of enablement is presented.

The Examiner previously asserted that the specification is not enabled for a therapeutic composition for the elicitation of a systemic, non-antigen specific immune response in a mammal comprising a liposome delivery vehicle and an isolated oligonucleotide containing no CpG motifs, or a method of using the same, as claimed.

The Examiner also alleged that for the reasons stated previously and presently the instant specification does not provide an enabling disclosure for a composition capable of eliciting a systemic immune response in a mammal, that would further be considered therapeutic, or a method of using said composition.

Applicants respectfully disagree with each of the Examiner's assertions for the reasons on record and for the following reasons.

Throughout the specification generally and more specifically in paragraphs [0094], [0102], [0104] and examples 12-15 characterized in paragraphs [0236]-[0242] and visually summarized in Figures 30-33 of the present specification Applicants have specifically enabled a therapeutic composition for the elicitation of a systemic, non-antigen specific immune response in a mammal comprising a liposome delivery vehicle and an isolated oligonucleotide containing no CpG motifs.

Paragraph [0094] (partially quoted below) specifically addresses the components of the therapeutic composition and how it was administered to produce a non-antigen-specific immune response as measured by the upregulation or production of various cells or mediators.

> One embodiment of the present invention is a method to elicit a systemic, non-antigen-specific immune response in a mammal. In this method, a therapeutic composition which includes: (a) a liposome delivery vehicle; and (b) an isolated non-coding, non-CpG containing, oligonucleotide is administered by intravenous or intraperitoneal administration to a

> mammal. It has been discovered that the non-coding, non-CpG containing oligonucleotides for use in the present invention are preferably in the range of about 10 to 500 nucleotides in length. While 10 nucleotides appears to be the lower limit in length the non-coding, non-CpG containing oligonucleotides may be greater than 500 base pairs, it appears however that there is no additional benefit derived from increasing length... Administration of such a composition by the method of the present invention results in the elicitation of a systemic, non-antigen-specific immune response in the mammal to which the composition is administered. As discussed above, this immune response additionally has strong, systemic, anti-tumor, anti-allergic inflammation (i.e., protective), and anti-viral properties. Such properties include the activation of NK cells (as measured by upregulation of NK cell markers, such as NK1.1, for example, **or by production of IFNα), production of Th1-type cytokines (e.g., IFNα)** and the non-antigen-specific recruitment and **upregulation of activity in mononuclear cells and T lymphocytes.** (Emphasis added)

Paragraph [0100] (partially quoted below) specifically addresses the therapeutic effect of the elicitation.

> Elicitation of an immune response in a mammal can be an effective treatment for a wide variety of medical disorders, and in particular, for cancer, allergic inflammation and/or infectious diseases.

Paragraph [0102] (partially quoted below) specifically addresses the non-antigen-specific immune response claimed.

> ...elicitation of a non-antigen-specific immune response (i.e., a non-specific immune response) includes stimulation of non-specific immune cells, such as macrophages and neutrophils, as well as induction of cytokine production, **particularly IFNγ production,** and non-antigen-specific activation of effector cells such as NK cells, **B lymphocytes and/or T lymphocytes.** (Emphasis added)

Example 12 described in paragraphs [0236]-[0238] in the specification and results articulated in Figure 30, specifically demonstrates that a therapeutic composition comprising a liposome delivery vehicle and an isolated oligonucleotide of either a 25, 50, 75, or 100mer containing no CpG motifs significantly elicits a systemic, non-antigen specific immune response in a mammal as measured by an increase T-cell activation.

Example 13 described in paragraphs [0239]-[0240] in the specification and results articulated in Figure 31, specifically demonstrates that a therapeutic composition comprising a liposome delivery vehicle and an isolated oligonucleotide of either a 25, 50, 75, or 100mer containing no CpG motifs significantly elicits a systemic, non-antigen specific immune response in a mammal as measured by an increase B-cell activation.

Example 14 described in paragraph [0241] in the specification and results articulated in Figure 32, specifically demonstrates that a therapeutic composition comprising a liposome delivery vehicle and an isolated oligonucleotide comprising a mixture of 50mer and 75mer containing no CpG motifs significantly elicits a systemic, non-antigen specific immune response in a mammal as measured by an increase IFNγ production.

Example 15 described in paragraph [024] in the specification and results articulated in Figure 33, specifically demonstrates that a therapeutic composition comprising a liposome delivery vehicle and an isolated oligonucleotide comprising a mixture of 50mer and 75mer containing no CpG motifs significantly elicits a systemic, non-antigen specific immune response in a mammal as measured by an increase IFNα production.

Based upon the data from above Examples the following objective conclusions were reached:

Figures 30 and 31 clearly show that all four oligo sequences (25, 50, 75 and 100 mer) have a significant effect on the % of CD8+/CD69+ (T-cell proliferation) or CD69+ (B-cell proliferation) and that the differences in effect between the 25, 50, 75, and 100 mer are likely insignificant from each other. On page 6 of the current office action the Examiner agreed that some activation of CD8+/69+ cells was detectable for oligonucleotides of 25 and longer lengths, the Examiner additionally argued that the response of the oligonucleotides of 25 and longer was inferior in all cases to the CpG containing oligonucleotide. Although it appears that that the non-CpG oligonucleotides may not provide as great as a response as the CpG oligonucleotide, the results may or may not be significantly different based on the individual data points for each of the four oligonucleotides. More importantly is that even if the CpG oligo response were significantly better for producing B and T-cell proliferation than the four oligonucleotides that

does not mean that the specification is not enabled for the four oligos which are statistically significant from the negative control.

Figures 32 and 33 clearly show that that non-CpG compositions as tested using a mixture of 50 and 75 mer oligonucleotides have a significant effect on IFNγ and IFNα.

In summary when comparing the CpG vs. non-CpG compositions, Figures 30 and 31 show that the CpG oligonucleotides possibly perform significantly better at some of the non-CpG data/comparison points (e.g., 25 mer, 50mer, etc); however Figures 32 and 33 demonstrate that non-CpG compositions as tested using a mixture of 50 and 75 mer oligonucleotides in the composition perform at least as well and significantly better than a CpG containing oligonucleotide when measuring for IFNγ and IFNα respectively. Therefore, when the data from examples 12-15 are viewed in their entirety the liposome composition comprising non-CpG oligonucleotides performs comparable to a 20mer oligonucleotide containing two CpG motifs.

Furthermore, it is restated that the specification and figures merely demonstrate the effect of the non-CpG oligonucleotides liposome compositions with CpG containing oligonucleotides for comparison/control purposes, it is not a claim limitation that the current composition is more effective than CpG containing oligonucleotides.

Based on the specification and the arguments on the record and above the specification as filed is clearly enabling for a therapeutic composition for the elicitation of a systemic, non-antigen specific immune response in a mammal comprising a liposome delivery vehicle and an isolated oligonucleotide containing no CpG motifs, or a method of using the same, as claimed.

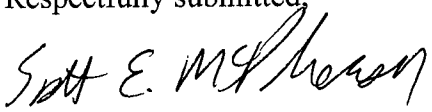
In light of the arguments on the record and above, the Examiner has failed to establish a prima facie case of lack of enablement. Accordingly, the present rejection may properly be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 858-350-6100.

Respectfully submitted,



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